TABLE 6—Continued

No.	Disease	Disease level		Normal level		Ref.
		AGP [mg/100 ml]	HSA [g/100 ml]	AGP [mg/100 ml]	HSA [g/100 ml]	
LXXXVIII	Pregnancy	In fetal serum, increase from 5 to 20 during gestation from week 15 to 40; in maternal serum, 70 ± 30	In fetal serum, increase from 1.5 to 3.5 during gestation from week 15 to 40; in maternal serum, 3 ± 0.5	25 ± 10 at birth 70 ± 30	3.5 ± 0.5 at birth 3 ± 0.5	284
LXXXIX	Pregnancy	49.7 ± 13.0 (maternal) 20.1 ± 9.4 (fetal)	3.56 ± 0.36 (maternal) 4.35 ± 0.40 (fetal)			357
XC	Pregnancy	15.3 ± 4.7 (fetal) 49.6 ± 6.5 (maternal)				585
XCI	Pregnancy	72.1 ± 2.7 (maternal) 31.6 ± 2.0 (fetal)				300
XCII	Pregnancy	54.5 ± 3.7	2.48 ± 0.76	56.6 ± 18.2	4.64 ± 0.71	140
XCIII	Pregnancy	In fetal serum, increase from 10 ± 5 to 30 ± 10 during gestation from week 28 to 40		30 ± 25 at birth and about 50 ± 25 on day 4		70
XCIV	Renal disease	135 ± 50	3.3 ± 1.0	86 ± 30	4.0 ± 1.0	206
XCV	Renal disease	165 ± 100 (complicated); 82 ± 40 (uncomplicated)	2.6 ± 1.5 (complicated); 3.5 ± 1.5 (uncomplicated)	66 ± 20	4.1 ± 0.8	409
XCVI	Septicemia	247 ± 45		64 ± 16		427
XCVII	Smoking	112 ± 63		92 ± 25		241
XCVIII	Smoking	84.3 ± 12.7	4.05 ± 0.29	62.8 ± 13.3	4.30 ± 0.23	46
IC	Traumatic injury	197 ± 100		70 ± 16	4.8 ± 0.4	153, 154
C	Trauma	Increase to 243 between days 10 and 14		70 ± 16		155
CI	Surgical trauma	Increase to 216 ± 35.2 on day 5	Decrease to 4.1 ± 0.3 on day 4	Preoperative, 111.5 ± 29.1	Preoperative, 4.8 ± 0.4	24
CII	Surgical trauma	200 ± 50		115 ± 25		129
CIII	Postoperative cholecystectomy	121 ± 22		64 ± 10		427
CIV	Hip replacement	Increase to about 180		80 ± 30		563
CV	Hernia repair	Increase to about 166 ± 28 on day 6, but increase to about 500 ± 100 when pneumonia as complication was diagnosed postoperatively	Decrease to about 2.59 ± 0.47 on day 6	Preoperative, 86 ± 21	3.43 ± 0.53	564
CVI	Surgical trauma	Increase to about 180		Preoperative, about 80 ± 40		163
CVII	Uremic patients	184 ± 62		Range, 62–142		226
CVIII	Chronic inactive pyelonephritis	Increase to 240 ± 40		62 ± 28		426
CIX	Nephritis	Increase to about 300		About 90		564
CX	Uremic patients	25 ± 15		25 ± 5		185
CXI	Uremic patients on hemodialysis	Before dialysis, 117.58 ± 36.65; after dialysis, 132.19 ± 37.12		98.32 ± 19.5		147
CXII	Vasculitis	30 ± 10		25 ± 5		185

growth factor receptor. Board et al. (64) reported recently, however, using the molecular cloning technique, that the homology between AGP and the epidermal growth factor receptor was poor.

Gamberg and Andersson (180) reported the presence of a membrane-bound form of AGP (with an apparent molecular weight of 52,000) on normal human lymphocytes, granulocytes, and monocytes (17–19). They demonstrated that this membrane protein is synthesized by lymphocytes and subsequently cleaved and released in the soluble serum form that has the normal molecular weight of 41,000. They concluded that this finding may

partially explain the increase in the AGP level in serum in many disorders involving leucocyte proliferations (17–19, 256, 257, 469).

There is also evidence that levels of AGP may change in the plasma of patients and several animals after treatment with defined drugs due to enzyme induction or inhibition of the AGP production (29, 33, 39, 84, 89–92, 99, 138, 301, 330, 386, 424, 425, 429, 432, 441, 531). This phenomenon has been reviewed by Greim (203). Both an increase and a decrease in the AGP level during drug therapy have been observed. Some studies with the same drug report contradictory results. Feely et al. (159) did not find an increase in the AGP level, due to hepatic enzyme induction of the AGP by rifampicin, as observed by Routledge et al. (441) and Delcroix et al. (138). Whereas Tiula and Neuvonen (531) and Olsson et al. (386) observed an increase in the AGP level after treatment with phenobarbital or carbamazepine alone, Bruguerolle et al. (89–92) observed a decrease in the AGP level only after treatment with a combination of these two drugs. Riva et al. (432) found an increase in the AGP level after carbamazepine treatment, in accord with the results of Tiula and Neuvonen (531) and Olsson et al. (386). Riva et al. (432) were the first to use serum from epileptic children and concluded that a modification of the serum AGP due to epilepsy itself cannot yet be ruled out and may be an explanation for the discrepancy in the results. Barbosa et al. (33) reported that anabolic steroids can both decrease and increase the AGP level, depending on their structures. As can be seen in table 6, nos. LXXXIV–XCIII and LXXX–LXXXI, the AGP level is decreased during pregnancy and during the use of oral contraceptives, due to the effect of estrogens. Reuss et al. (429) reported on a model that can be used to predict the AGP level during perazine therapy. Benedek et al. (46) found that smoking also raises the AGP levels, possibly due to an alteration in the serum protein chemistry or due to the accumulation of endogenous or exogenous substances (i.e., basic compounds in the smoke itself).

Many of the discrepancies in the literature dealing with changed AGP levels after drug therapies appear to be due to attempts by investigators to draw a single conclusion from studies involving different species and different dosing regimens.

B. Several Other Biological Activities of Alpha-1-acid Glycoprotein

Many other biological properties of AGP are discussed in the literature: its immunological response behavior during several pathological states (50, 57, 110–112, 115, 253, 262, 405, 589); its protective effect against neonatal sepsis (57, 405); its inhibition of platelet aggregation (20, 21, 35, 124, 280, 342, 375, 378, 503, 507, 514, 569, 571); its interaction with collagen (124, 168); its growth-promoting effect for Hela and H-6 cells (325, 326); its involvement in the T_3-T_1 antigen-specific pathway of T-cell activation (511); its interaction with phospholipid membranes (110–112, 324–326, 368–372); its occurrence as carrier of a cofactor in the lipoprotein lipase reaction (509); its inhibition of phagocytosis (388, 389); its inhibition of the multiplication of malaria parasites (174, 175, 208); its interaction with vitamin B_{12} (224); its inhibition of neutrophil activation (125); its prolongation of the survival of skin homografts (361, 388); and its histamine binding capacity (103).

Bennett and Schmid (50) reported that the effectiveness of immunosuppression is enhanced for agalacto/asialo derivatives of AGP; this points to the importance of the carbohydrate moiety in the immunoregulatory function of AGP. Cheresh et al. (112) studied sera from cancer patients and found a positive correlation between the AGP level and its immunosuppressive capacity. They observed the inhibitory effect of breast cancer serum on mitogen-induced blastogenesis of normal lymphoid cells. Cheresh et al. (111) further reported that nonspecific immunosuppression is due to electrostatic forces between sialic acids groups of AGP and phospholipids; however, no change in the lipid packing is involved because the phase transition temperature did not change. Jamieson et al. (253) found that AGP is located at the inflammatory site and may be involved in some aspects of the inflammation process.

Andersen and Eika (21) reported that totally desialylated AGP lost much of its capacity as inhibitor of the platelet aggregation, whereas Costello et al. (124) observed an increase in this effect in the presence of desialylated AGP. Barclay et al. (35) and Spragg et al. (507) observed that the inhibition of the hemagglutination was dependent on the shape and the size of the AGP polymers.

Franzblau et al. (67) reported that the interaction of AGP with collagen resulted in the formation of fibrous, long spacing fibers of collagen; presumably this process is also involved in the wound healing.

Maeda et al. (325, 326) found that AGP facilitated the passage of erythrocytes through membranes. AGP increased the bilayer thickness of liposomes and decreased the membrane permeability for ions (868, 369). More recently Neitchev (370) reported that the decreased permeability of liposomes after the addition of AGP was dependent on the AGP/protein ratio and was due to the interaction of AGP and protein with lipids, which in turn led to electrostatic changes in the membrane lipid region and membrane surface. Furthermore AGP could play the role of active modifier changing the membrane selectivity (371, 372).

Friedman et al. (174, 175) found that AGP could inhibit invasion by malaria parasites. However, Gupta et al. (208) could not confirm these inhibitory effects of AGP.

Chachaj et al. (103) studied the histamine-binding properties of plasma proteins. Their results suggested that human serum contains three histamine-binding

fractions, identified as orosomucoid and two glycoproteins belonging to the α_1-globulin group. Parrot et al. (393) and Laborde et al. (295) reported earlier that serum from patients with allergic disorders showed an impaired ability to bind histamine. The increase in the binding to histamine in allergic diseases might perhaps be ascribed to an increase in AGP, as has often been reported in other inflammatory diseases, but the possible existence of such a correlation has not been studied so far.

These many diverse activities are difficult to interpret. By careful study of the papers cited it may become apparent that many of the reported activities do not occur in a regulatory fashion at physiological concentrations of AGP, and they are therefore unlikely to be functional (177, 342, 451). In view of the purpose of this review, we will not discuss these activities in detail here.

IV. Interactions of Drugs with Alpha-1-acid Glycoprotein

HSA, AGP, and lipoproteins (LIPO) are the most important plasma proteins responsible for the binding of drugs in plasma. HSA binds in particular acidic and neutral drugs, whereas AGP and LIPO bind mainly basic drugs (82, 83, 194, 195, 358, 377, 406–408, 412, 414, 415, 450, 546). Table 7 gives a survey of studies which deal with the binding of drugs to AGP. Most of these drugs are basic ones with pK values of 8 or higher, which implies that these drugs are positively charged at physiological pH. Some of the drugs, such as phenylbutazone, phenobarbital, and the anticoagulants, are acidic and may be partially or totally negatively charged at neutral pH. Some other drugs, such as the steroids, diazepam, and carbamazepine, are neutral. From more recent studies dealing with the binding of drugs to AGP, it follows that other drugs not included in table 7 have an affinity for AGP; e.g., aminopyrine (156), amoxapine (160), bupropion (160), maprotiline (160), nomifensine (160), trazodone (160), drugs with a quaternary ammonium group (498), ritodrine (204), doxazosin (160), trimazosin (160), binedalin (358, 359), amsacrine (399), apazone (544) and SKF 525 A (45).

In this section the binding of drugs to AGP will be discussed. Section IV A will deal mainly with the relation between the varying concentration of AGP and its drug binding properties. In section IV B, the binding of basic and neutral drugs to isolated AGP is reviewed. A small section (IV C) is devoted to the binding of acidic drugs to AGP. The molecular details of the drug binding to AGP will be discussed in section IV D. In section IV E, it will be demonstrated that the results of binding studies can be strongly influenced by the experimental circumstances.

A. Binding of Drugs to Alpha-1-acid Glycoprotein in Vivo

Since the end of the sixties it has become clear that AGP can function as a drug carrier for steroids (181, 182, 565). Later it was demonstrated that AGP also has high binding affinity for several basic drugs (396, 406–408) and, as has been shown recently, for some acidic drugs as well (249, 544, 545).

Variations have been observed in the binding of basic drugs in plasma (5, 396, 406–408, 538). This has been shown to be due to variations in plasma protein concentration, particularly in several disease states. Changes in the plasma protein concentrations have been reported for drug binding plasma proteins, particularly for HSA, AGP, and LIPO (406–408, 445, 538, 546). From binding studies it follows that HSA accounts mainly for the binding of acidic and neutral drugs, whereas AGP and LIPO associate more readily with basic drugs (194, 377, 406–408, 412, 414, 415, 546). It has become clear that the drug binding capacity of AGP, especially for basic drugs, can be of the same order as or even higher than that of HSA. This implies that the large variation in the AGP level in plasma observed during several physiological and pathological conditions can have a profound effect on drug concentrations in the blood. This correlation between the extent of drug binding and the AGP concentration in plasma will be discussed in the first part of this section.

It can be concluded from the literature (194, 377, 406–408, 412, 414, 415) that HSA, LIPO, and AGP are the most important plasma proteins that play a role in plasma drug binding. This means that the total drug concentration in plasma (c^{plasma}) can be given by equation 1:

$$c^{plasma} = c_{free} + c^{AGP}_{bound} + c^{HSA}_{bound} + c^{LIPO}_{bound} \qquad \text{equation 1}$$

where c_{free} is the free concentration of the drug in plasma, and c^{AGP}_{bound}, c^{HSA}_{bound}, and c^{LIPO}_{bound} represent the concentrations bound to AGP, HSA, and LIPO, respectively. If the binding of drugs to proteins can be described by Scatchard plots (196a, 349, 457), equation 2 can be used for the calculation of the drug concentrations bound to several components (c^i_{bound}) in plasma:

$$c^{plasma}_{bound} = \sum c_{i\,bound} = \sum \frac{n_i P_i K_i c_{free}}{1 + K_i c_{free}} \qquad \text{equation 2}$$

where n_i, P_i, and K_i are the number of binding sites, the plasma protein concentration, and the affinity constant of component i in plasma, respectively. Note that, in this review, K_i is an association constant not a dissociation constant.

The use of equation 2 has been criticized in the literature (95). In the discussion that follows, it will become clear that equation 2 will apply to situations in which the average number of occupied binding sites is much less than one. In that case, there will no longer be objections to the use of this equation. Equations 1 and 2 describe the system completely. If protein concentrations, the number of binding sites, and the binding constants are known, then c_{free} can be calculated at a